Remarks

Claims 1-4 are pending. Claims 1-4 have been amended. Claims 5-51 have been cancelled. New Claims 52-66 have been added. Support for these new claims is found in the specification and claims as filed especially Claims 5-19 as filed.

Rejection Under 35 U.S.C. § 103

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *von Mensdorff-Pouilly* et al. (Eur J Cancer 1996 32 :1325-1331; "Mensdorff-Pouilly") or *Gourevitch* et al (Br J Cancer 1995 72 :934-938; "Gourevitch") in view of *Petrarca* et al. (Eur J Cancer 1996 32 :2155-2163; "Petrarca"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 2143.

Mensdorff-Pouilly and Gourevitch disclose the detection of circulating immune complexes containing polymorphic epithelial mucin (PEM) encoded by MUC-1 in sera of patients suffering from various stages of cancer. The complexes are detected in the patients' sera using **monoclonal** antibodies to PEM. Neither Mensdorff-Pouilly nor Gourevitch disclose the utility of **autoantibodies** in their diagnostic procedures. Similarly, although

Petrarca discloses the production of human MUC-1 antibodies, Petrarca fails to demonstrate the utility of autoantibodies in an assay for detecting a cancer-associated target antigen in a patient sample.

Applicants have discovered that human anti-MUC-1 **autoantibodies** show substantially improved **sensitivity** over murine **monoclonal** antibodies such as those used by Mensdorff-Pouilly or Gourevitch. (See page 4, lines 1-19 of the present specification). Example 2 of the present specification presents comparative data demonstrating the differences between murine monoclonal antibody B55 and autoantibodies isolated from cancer patients (see pages 14-15 of the present specification). In particular, the specification states on page 15, lines 1-5 that:

> "...the sensitivity of the autoantibodies for cancer-associated MUC1 is much greater than that observed for the monoclonal B55 antibody. Furthermore, antibodies produced by lymphocytes from normal patients did not show this profile."

The autoantibodies described by applicants also display a higher **affinity** for target antigen. Monoclonal antibodies were used in Example 2 (See p. 13 of the present specification) to isolate MUC1 protein from healthy individuals, cell lines and cancer patients. Monoclonal antibodies do not distinguish between normal and cancer-associated MUC1 isoforms. The claimed autoantibodies provide a means to distinguish between normal and pathological isoforms of a protein. The specification states on page 15, lines 11-20 that:

> "The autoantibodies show high specificity for MUC1 present in the serum of patients with cancer and have almost no affinity for MUC1 isolated from healthy individuals or from the breast cancer cell line

> AR75-1. Furthermore, the affinity of the autoantibodies for MUC1 protein associated with either primary breast cancer or advanced breast cancer is much higher tha[n] measured for B55." (sic)

This increased sensitivity and affinity provides superior means to detect cancer-associated markers and reduces the occurrence of false positive test results. Such an improvement in diagnostics could not have been predicted or developed absent the teachings of the present specification thereby supporting a case of non-obviousness.

Petrarca provides no motivation to combine with either Mensdorff-Pouilly or Gourevitch and in fact **teaches away** from combining with either Mensdorff-Pouilly or Gourevitch. The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Petrarca's results describe human autoantibodies that have different immunological characteristics from standard murine monoclonal antibodies thereby discouraging one of ordinary skill from using the autoantibodies in a detection assay. Figure 1b of Petrarca demonstrates the different epitope binding properties of autoantibodies as compared to monoclonal antibodies but does not disclose improved or reduced antigen binding over monoclonal antibodies. One of ordinary skill could not predict how autoantibodies would perform compared to monoclonal antibodies in an assay because of the different antigen binding domains. Petrarca discloses that the PPAH binding motif is distinct from the PDTR sequence, which is immunodominant. (p. 2158, col. 2). One of ordinary skill in the art would understand that the **monoclonal** antibodies bind better and would therefore be better

suited to a diagnostic assay. Petrarca further discloses that "all human antibodies are IgM" with weak reactivity and low affinity (p. 2161, col. 2). Petrarca therefore teaches away from the applicants' findings and claimed invention. One of ordinary skill would not be motivated to use **autoantibodies** because there is no expectation that they would perform as well as **monoclonal** antibodies in a detection assay based on the teaching of Petrarca. Applicants demonstrate that despite this negative teaching, the autoantibodies unexpectedly give an improved assay because of their increased sensitivity and affinity.

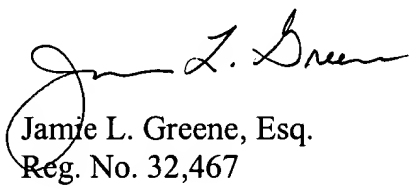
Absent the teachings of the present specification, there would be no reasonable expectation of success that autoantibodies could be used in an assay to detect a cancer-associated target antigen in a patient sample with such specificity and affinity. Conversely, applicants teach that autoantibodies outperform monoclonal antibodies and provide such improved binding characteristics as to provide a highly sensitive method to detect cancer-associated markers. The binding properties of autoantibodies are not disclosed by the prior art nor is there any disclosure of an assay to specifically distinguish between markers found in healthy individuals and cancer patients. In view of these facts, a finding of non-obviousness is respectfully requested.

CONCLUSION

The foregoing is a complete response to the Office Action mailed May 26, 2004. Applicant respectfully submits that the present application is in condition for immediate allowance. An early notification is earnestly solicited. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855. If the Examiner has any questions, or further issues remain to be resolved, the Examiner is requested to contact the undersigned at (404) 745-2473.

Allowance of Claims 1-4 and 52-66 is respectfully solicited.

Respectfully submitted,



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